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# Oral Contraceptive Estrogen Content and Adverse Effects: Has a Dose-Response Relationship been Established?


## SUMMARY

The 1985 Health and Welfare Canada *Report on Oral Contraceptives* recommended oral contraceptives (OCs) containing 30–35 mcg of estrogen rather than 50 mcg as the preferred dosage for contraception. Many family physicians may regard these guidelines as mandatory when prescribing OCs, because of a presumption that pills of 50-mcg estrogen content carry a higher risk of disease. In this article, the epidemiologic evidence pertaining to a dose-response relationship between the estrogen dose of oral contraceptives and disease is critically reviewed. The review indicates that there is no incontrovertible evidence to support such a relationship. Implications of the recommendations in the Report for physicians and patients are discussed. (*Can Fam Physician* 1987; 33:445–460.)

## SOMMAIRE

Santé et Bien-être social Canada, dans son Rapport sur les contraceptifs oraux publié en 1985, recommandait l'utilisation de contraceptifs oraux content 30–35 mcg d'oestrogènes plutôt que 50 mcg comme posologie contraceptive. Nombreux sont les médecins de famille susceptibles de considérer ces recommandations comme obligatoires, à cause de la présomption que les anovulants contenant 50 mcg d'oestrogènes présentent un risque accru de maladie. Cet article procède à une revue critique de l'évidence épidémiologique concernant le lien dose-réponse existant entre la quantité d'oestrogènes contenue dans les contraceptifs oraux et la maladie. Cette révision indique qu'il n'existe aucune preuve incontestable pour appuyer un tel lien. L'auteur discute les implications des recommandations de ce rapport pour les médecins et leurs patientes.


**Key Words:** oral contraceptives, dose-response relationship, contraception

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IN THEIR 1985 REPORT, the Special Advisory Committee on Reproductive Physiology to the Health Protection Branch, Health and Welfare Canada, made specific and firm recommendations about the dosage of estrogen that should be used for contraception:

> The recommended dosage of estrogen for contraception is 30–35 mcg. Use the lowest dosage of any given progestogen that will provide for contraception and good cycle control.
>
> Oral contraceptives containing 50 mcg of estrogen should be used only when good cycle control cannot be attained with compounds containing 30–35 mcg of estrogen.[1]

The Special Advisory Committee has acknowledged that it is too soon to determine if prescribing oral contraceptives (OCs) containing less than 50 mcg of estrogen will reduce the number of adverse effects associated with their use.[1] Nevertheless, much of the relevant literature either implies or actually states that pills containing less than 50 mcg of estrogen are safer than OCs with a higher estrogen content.[2] This assumption would be supported if there were solid evidence of a dose-response relationship between disease and the dosages of estrogen in OCs. However, a review of the published reports discovers no incontrovertible evidence to support such a conclusion.

In this article, our aims are twofold: to evaluate the information available in English-language publications on the effects of estrogen dosage in OCs on the risk of disease, and to examine the implications that the Committee's recommendations might have for practising physicians.

## Evaluation of the Literature

In assessing the published findings, it is important to keep in mind some general problems that make studies of OC effects extremely difficult, if not impossible:

- Because low-dose (30–35 mcg) OCs have been in use for only about 12 years, they have not been studied as thoroughly as have 50-mcg pills. Therefore more information is available about the higher-dose pills.
- It is difficult to assess the effect of estrogen because of the presence of the progestogen component in OCs. Progestogens are used in different dosages and vary in their biological effects. They may have anti-estrogenic, estrogenic, or androgenic effects, in addition to progestational ones. Moreover, the effects of estrogens and progestogens are interactive when these hormones are administered in combination.[3]
- The methodologies for assessing progestogen potencies have not been adequately developed or standardized,[4] and no method currently exists for comparing the potencies of proges-

**Table 1**
**Oc Estrogen Dose and Disease:**
**Adverse Drug Reactions Studies (EE=ethinylestradiol; ME=mestranol)**

| Author | Disease | Estrogen Dosage (mcg) | Dose-Response Relationship |
|---|---|---|---|
| **Venous Thromboembolism** | | | |
| Inman et al. 1970 | Fatal pulmonary embolism | ME 50, 75–80, 100, 150 | Positive trend |
| | Non-fatal pulmonary embolism | " | Positive trend |
| | Deep vein thrombosis lower limb | " | Non-significant positive trend |
| | Other venous thrombosis of the lower limb | " | No difference |
| | All venous thrombosis | " | Positive trend |
| Böttiger, 1980 | | | **1966–1970** |
| | Venous thromboembolism | "estrogen" 50, 75 or more | Positive trend |
| | Superficial thrombophlebitis | " | positive trend |
| | | | **1966–70 & 1973–1977** |
| | Venous thrombo-embolism | "estrogen" 50 or fewer | Positive trend |
| | Superficial thrombophlebitis | " | Positive trend |
| Meade et al. 1980 | Pulmonary embolism | EE 30, 50 | No difference |
| | Deep vein thrombosis | " | No difference |
| | Superficial venous thrombosis | " | No difference |
| Kierkegaard, 1984 | Deep venous thrombosis | ME 50, 75–100 | Positive trend |
| | | EE 30–35, 50 | Positive trend |

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togens in combination with an estrogen.[1,5] As a result, much confusion and controversy have arisen in the published reports on the meaning and measurement of progestogen potency.

The Special Advisory Committee made it clear in its Report that its members did not give scientific credence to the reported findings on progestogen effects. Nevertheless, even though the confounding effect of progestogen cannot be measured, it does exist, and therefore cannot be ignored when an attempt is made to interpret the data on the effects of estrogen dosage.

- Several sources of bias are apparent in all the different types of studies in which the relationship between estrogen dose and adverse effects has been investigated. These studies fall into four basic types:
- reported trends in adverse drug reactions;
- temporal trends in disease-specific mortality or morbidity rates;
- case-control studies;
- cohort studies. Specific kinds of bias may affect different types of studies to varying degrees.
- Low-dose estrogen pills are most likely to be used by younger OC users. Since major circulatory disease occurs very rarely in young women, it is unrealistic to expect the existing information about adverse effects to provide data on which to base definitive conclusions. Furthermore, the increased morbidity or mortality from circulatory disease reported in OC users with existing risk factors for such diseases has led physicians to apply stricter selection criteria than they once did before prescribing OCs. Consequently, most women who use OCs are healthy, and have no known risk factors for circulatory disease. These factors will tend to reduce still further

**Table 1 (Continued)**

| Author | Disease | Estrogen Dosage (mcg) | Dose-Response Relationship |
|---|---|---|---|
| **Arterial Thromboembolism** | | | |
| Inman et al., 1970 | Cerebral thrombosis | ME 50, 75–80, 100, 150 | Positive trend |
| | Coronary thrombosis | " | Positive trend |
| Meade et al., 1980 | Ischaemic heart disease | EE 30, 50 | Positive trend |
| | Stroke | EE 30, 50 | No difference |
| | | | **1966–1970** |
| Böttiger, 1980 | Arterial thromboembolism | "estrogen" 50, 75 or more | No difference |
| | | | **1966–1970 & 1973–1977** |
| | Arterial thromboembolism | "estrogen" 50 or fewer 50 or more | No difference |
| **All Arterial and Venous Thromboembolism** | | | |
| Inman et al., 1970 | All arterial and venous thromboembolism | EE 50, 100 | Positive trend |
| **Hypertension** | | | |
| Meade et al., 1980 | Hypertension | EE 30, 50 | No difference |
| Böttiger, 1980 | Deaths among women taking OCs | "low estrogen dose" 1973–1977, | No difference |
| | | "high estrogen dose" 1966–1970 | No difference |

the previously observed risks of circulatory disease, and to make an evaluative comparison between 50-mcg and 30-mcg OCs even more difficult.

## Adverse Drug Reactions

Inman,[6] Meade,[7] Böttiger[8] and Kierkegaard[9] all used reports of adverse drug reactions to assess the relationship between OC estrogen dosage and disease. (See Table 1.)

*Venous thromboembolic diseases*

The first report that claimed to establish a relation between the dose of estrogen and the risk of thromboembolic disease (arterial and venous) was published in Inman et al.[6] This report was based on data provided by the United Kingdom Committee on Safety of Drugs relating to adverse reactions in women using OCs for conception control. Between 1965 and 1968, the lowest dose of estrogen then in use was 50 mcg. Inman et al.[6] also reported a similar association for pulmonary embolism and venous thrombosis of the lower limb in Sweden and Denmark, on the basis of data supplied by those countries' committees on adverse drug reactions.

The problems apparent in the data were as follows:

- *Gross under-reporting of adverse reactions by physicians.* The authors ot the report estimated that the data available represented less than 10% of the incidents that occurred. They evaluated the data for any evidence of selective reporting bias among doctors, or for geographic variation in the level of the reporting. They were convinced that the small sample was an unbiased representation of the physician population.

Because of evidence of clustering of reports from family-planning clinics during the reporting period, these reports were excluded from the analysis. Bias from this exclusion would result only if family-planning clinics prescribed a relatively large proportion of products containing a high dose of estrogen. It was unlikely, the authors reasoned, that this had occurred. In fact, they used a circular argument: high-dose products cause major adverse reactions; since only minor reactions were observed in the data of the planning clinic, few high-dose products must have been prescribed. No data were actually examined.

- *A spurious dose response would be observed if high estrogen doses were used mainly by older women*, since these women would have a higher risk of disease. But the authors found no association between age and the dosage of OC used.
- *An unexplained discrepancy in the results* that showed a low risk associated with preparations containing norethynodrel (a progestogen with estrogenic activity), and a high risk associated with a preparation containing a low-estrogen dose (50 mcg) and a high dose of megestrol acetate (a progestogen with progestational activity). The authors' comment was that factors other than the dose of estrogen seemed to be operating: the most likely of these was some influence of the progestogens.

Despite the deficiencies and inconsistencies in the data, the results of this analysis on the relation between estrogen dose and thromboembolism were accepted as proven; they immediately led to a worldwide reduction in the dose of estrogen in combination OCs.

The "natural experiment" of gradually decreasing estrogen dosage in preparations marketed in Sweden was used by Böttiger et al.[8] to determine whether the association between OC estrogen dosage and thromboembolic diseases noted by Inman et al.[6] could be extended to a comparison of 50- and 30-mcg estrogen. Böttiger's team examined reports of adverse drug reactions and confirmed the dose effect previously described by Inman et al. 1966–1970. They also estimated that the average risk for a reported thromboembolic disorder had declined by a factor of more than three between 1966–1970 and 1974–1977. Despite the marked reduction in venous thromboembolism over that period, which the author attributed to decreasing estrogen doses, Böttiger admitted that the influence of such factors as changes in prescribing habits and increased knowledge about risk groups was impossible to evaluate. Over the same period of 1966–1977, he found that mortality associated with OCs as reported in Swedish reports of adverse reactions remained constant.

Meade[7] assessed the relative safety of 50- and 30-mcg estrogen OCs while he was investigating the relationship between OC progestogen dose and disease. He reviewed reports to the U.K. Committee on Safety of Drugs from 1964–1977 (excluding those reports that mentioned previous thromboembolic episodes or predisposing conditions), and found no statistically significant difference between OCs containing 50 mcg or 30 mcg of ethinyl estradiol for pulmonary embolism or for superficial or deep venous thrombosis (DVT).[7] Meade was aware of, but unable to control for, the confounding effect of the progestogens.

Kierkegaard[9] studied cases of acute DVT among OC users. These cases were identified from hospital records and Swedish reports of adverse drug reactions for 1966–1981, in order to determine whether the previously reported dose-response relationships could have arisen from bias. The author did observe a dose-response relationship between estrogen dose and DVT for mestranol (50–100 mcg) and ethinyl estradiol (30–50 mcg) OCs. Kierkegaard, however, also found a number of problems with the data.

- The method of diagnosis for DVT changed over the interval and was associated with the estrogen dose of the OC. Women who were prescribed low-dose OCs were more likely to have a diagnosis made on the basis of phlebography or autopsy than were women taking high-dose OCs.
- Examination of the hospital study, and the reporting of adverse reactions from it, show that the chance of a diagnosed case being reported declined over time (i.e., reporting practices *did* change over time).
- Marked geographic variations had occurred in the reporting of adverse drug reactions.
- There was clear evidence of confounding by age, with older women being prescribed higher-dose OCs.
- The 50-mcg ethinyl-estradiol OCs contained different types and dosages of progestogens.

Kierkegaard therefore concluded that the observed association

> was secondary to differences in the diagnostic standard of DVT, to differences in reporting policies . . . and to an age difference between women on low-oestrogen pills and those on high-oestrogen pills and is thus due to bias.

Kierkegaard's study clearly demonstrates, therefore, that because of important biases in the data, conclusions based on the Swedish Adverse Drug Reactions Reports on the association between venous thromboembolic disease and OC estrogen dosage lack validity. It is reasonable to believe that

reports from other countries of adverse drug reactions may be similarly biased.

*Arterial thromboembolism*

The initial report by Inman et al. identified a statistically significant trend of increased cerebral and coronary thrombosis in women taking OCs containing 150, 100, 75–80 and 50 mcg of mestranol.[6] For OCs containing 100 mcg of ethinyl estradiol as compared with 50 mcg, the difference was significant only when all arterial and venous thromboembolisms were combined.[6] For 1966–1970, Böttiger[8] found no differences in the occurrence of cerebral or coronary thromboembolism or of all arterial sites combined between women taking OCs containing 75 mcg or more of estrogen and those taking 50 mcg of estrogen. Between 1966–1970 and 1973–1977 (when 30–35 mcg OCs became widely used in Sweden), no change occurred in the reporting of arterial thromboembolic diseases. The deficiencies and inconsistencies of these data, as previously identified with respect to venous thromboembolism and estrogen dose, apply equally to the findings on arterial disease and estrogen dosage.

Meade,[7] in his study of OC progestogen dose and disease, also compared women taking 30- or 50-mcg ethinyl estradiol OCs. In the 30-mcg group, he noted a significant decrease in ischemic heart disease, but not in stroke. Problems also exist in these data that may influence observed dose-response effects of OC estrogen on arterial disease:

- There was evidence that women prescribed 30-mcg OCs were younger than the women for whom 50-mcg preparations were prescribed.
- It was not possible to control for smoking, an important and potentially confounding factor.
- Although Meade thought that the reporting of adverse drug reactions was unlikely to have been biased with respect to the progestogen doses, he commented that "until now concern has centered almost entirely on the oestrogen dose." One must consider, therefore, that the observed association between estrogen dose and disease may have resulted from biased reporting related to the prescribed dosages of estrogen.

*Hypertension*

Neither Inman[6] nor Böttiger[8] examined reports of hypertension. Meade,[7] who did so, found no differences between women using 50-mcg ethinyl-estradiol OCs and those using 30-mcg ethinyl-estradiol OCs.

## Mortality and Morbidity Trends

Two studies have used mortality and morbidity trends to establish a relationship between estrogen dose and diseases. (See Table 2.)

*Pulmonary embolism*

Because the estrogen content of OCs has declined over time, mortality rates from pulmonary embolism and infarction in Caucasians in the United States were examined over four time intervals between 1961 and 1972.[10] In 1964–1966, 15–34-year-olds showed an increase in the female-male ratios of deaths from these causes as compared to the preceding interval, which was followed by a decrease. The temporal variations observed by Sartwell[10] are consistent with differences attributed to changes in the estrogen content of OCs over the period.

*Thromboembolic diseases*

Böttiger,[8] on the other hand, found no changes in mortality rates for cerebral thrombosis, myocardial infarction, arterial thrombosis or deep venous thromboembolism in Sweden, between 1966–1968 and 1975–1977, despite the decreasing dosages of estrogen in the OCs that were then available. Between 1966–1968 and 1974–1976, he did find an apparent, but not statistically significant, decline in morbidity caused by thromboembolism requiring the patients' hospitalization.

These studies were examined in terms of Feinstein's criteria[11] for establishing a causal relationship between an exposure and a disease:

- The temporal precedence criterion for causation states that the exposure of interest must precede the outcome. Such precedence can be inferred in temporal trend studies only if the initial incidence of the disease is low but increases with increasing exposure to the agent of interest. The findings of Sartwell[10] and Böttiger[8] are inconsistent in this regard.
- There must be evidence that the affected women were actually exposed (i.e., had used the OC and had used various doses in the different time intervals). Böttiger's morbidity study determined that the women were indeed exposed to the OC, although the author made no comments about the dosages involved. Evidence of actual exposure was not available for the mortality studies done either by Böttiger or by Sartwell.
- There must be equal prognostic susceptibility in developing an outcome event both in terms of demographic characteristics (e.g., age, gender, race, socio-economic status) and also in terms of clinical characteristics. It was not possible to control for prognostic susceptibility in either of the mortality studies, although Böttiger did attempt to control prognostic susceptibility in his morbidity study by excluding those women with disorders

**Table 2**
**Oc Estrogen Dose and Disease: Mortality & Morbidity Trends**

| Author | Disease | Mortality/ Morbidity Trends |
|---|---|---|
| Sartwell, 1976 | Fatal pulmonary embolism/ infarction | Consistent with dose-response relationship |
| Böttiger, 1980 | Fatal thromboembolism (Nat'l Mortality data) | No change |
| | Women hospitalized with thrombo-embolism | Non-significant decline consistent with dose-response relationship |

that might predispose to thromboembolism. However, changes in the many other factors that also occur over time (e.g., patterns of smoking, diet, and exercise) may also influence trends in mortality or morbidity.

- There must be equal probability of detecting an outcome event for each study group. Known inaccuracies in the certification of cause of death occur, as do differences in diagnostic techniques over time and by place. It is quite possible that as compared with OC non-users, OC users were subjected to more intensive investigations, including autopsy, and were therefore more likely to have had their disease diagnosed and certified as a cause of death.
- The studies were unable to control for migration.

## Case-Control Studies

Four case-control studies[12–15] have looked for an association between OC estrogen dose and vascular diseases, but none of them found a statistically significant association. (See Table 3.)

*Total thromboembolic disease*

In order to determine whether the risk of thromboembolism was decreased by the reduction of OC estrogen content below 100 mcg, Stolley et al.[13] performed a multicentre case-control study of thromboembolic diseases in women aged 15–39 who were hospitalized between 1970 and 1973. The team observed a tendency for users of OCs containing 100 mcg or more, as compared to less, than 100 mcg of estrogen to show an increased risk for all thromboembolic diseases combined (i.e., pulmonary embolism and infarction; phlebitis and thrombophlebitis of the lower limb; arterial embolism; and thrombosis, including myocardial infarction, but excluding cerebral thrombosis). However, the confidence limits of the risk estimates overlapped considerably.

The investigators tried to obtain equal prognostic susceptibility between cases and controls by matching subjects for race, marital status, and age, and by making further adjustments for other factors in multivariate analysis. Cases and controls were similar in the matter of smoking. Equal prognostic susceptibility on the basis of age may not have been achieved, however, because the age strata were wide. The authors admitted their inability to control for the confounding effect of the progestogens.

*Arterial thromboembolism*

The Collaborative Group for the Study of Stroke in Young Women[12] was unable to make a direct comparison between 100-mcg and 50-mcg OCs and the occurrence of stroke in a case-control study of OC use, other risk factors, and stroke. This was because the 100-mcg preparations contained mestranol, while the 50-mcg preparations contained ethinyl estradiol. This would have produced confounding by estrogen type. However, analysis of the data for odds ratios associated with individual brands of OCs showed no statistically significant variations for either hemorrhagic or thrombotic stroke.

In the course of a U.S. study of OC use and cigarette smoking among women aged 25–49 who were hospitalized with myocardial infarction, the authors compared OCs containing more than 50 mcg, 50 mcg, or less than 50 mcg of estrogen.[14] They found no evidence that the risk of infarction varied according to the dosage of mestranol or ethinyl estradiol.

**Table 3**
**OC Estrogen Dose and Disease:**
**Case-Control Studies (EE=ethinylestradiol; ME=mestranol)**

| Author | Disease | Estrogen Dosage (mcg) | Dose-Response Relationship |
|---|---|---|---|
| Stolley, 1975 | All venous & arterial thromboembolism combined (includes acute MI, but not CVA | "estrogen" fewer than 100, 100 or more | Consistent with a positive trend, but not significant |
| Collaborative Group, 1975 | Stroke | Data inadequate for dose | Unable to assess |
| | | "Brand" of OC | No relationship |
| Shapiro, 1979 | Non-fatal MI | "Estrogen" ME or EE fewer than 50, 50, 50 or more | No difference |
| Adam, 1981 | Fatal MI | "Estrogen" fewer than 50, 50 | No difference |

An additional failure to find a dose-response relationship between OC estrogen dose and myocardial infarction was reported by Adam.[15] U.K. women who had used OCs containing less than 50 mcg of estrogen had the same risk of fatal myocardial infarction as women who had used OCs containing 50 mcg of estrogen. The authors were aware of, but unable to control for, confounding by progestogens.

## Cohort Studies

Five reports of cohort (follow-up) studies investigating the relationship between OC estrogen dose and disease are listed in Table 4. Three of these five studies are based on the same population.

*Venous thrombosis*

The first published cohort study was the 1974 report of the Royal College of General Practitioners (RCGP) Oral Contraception Study. This study found that evidence of a trend for rates of superficial thrombosis of the leg and total venous thrombosis was greater for women taking OCs containing 75 mcg or more of estrogen as compared to those taking 50 mcg OCs.[16] The data, however, suffer from a number of flaws:

- Confounding by progestogens undoubtedly occurred.
- the authors stated that the incidence of DVT of the leg showed no association with age, but that such an association did exist for superficial venous thrombosis. Since age was associated with the incidence of superficial venous thrombosis, bias would result from variations by age in the dosages of estrogen prescribed. Such variations have been observed by other investigators.[7, 9, 17] It would appear that age standardization was not per-

**Table 4**
**Oc Estrogen Dose and Disease: Cohort Studies**

| Author | Disease | Estrogen Dosage (mcg) | Dose-Response Relationship |
|---|---|---|---|
| **Venous Thromboembolism** | | | |
| RCGP, 1974 | Superficial venous thrombosis | "estrogen" 50, 75–80, 100–150 | Consistent with positive trend |
| | DVT | 100–150 | Trend not apparent |
| | Total venous thrombosis | 100–150 | Consistent with positive trend |
| RCGP, 1978 | Superficial venous thrombosis | "estrogen" 50, 75–80, 100–150 | Positive trend |
| | DVT | 100–150 | No difference |
| Porter, 1982 | Venous thrombo-embolism | "estrogen" fewer than 50, 50–80, 100 or more | No difference |
| Vessey et al., 1986 | DVT or pulmonary embolism | "estrogen" 50 mcg or more | Consistent with dose effect, data too few to confirm |
| | Superficial venous thrombosis | <50 mcg | |
| **Hypertension** | | | |
| RCGP, 1974 | Hypertension | "estrogen" 50, 100 | Negative trend (attributed to estrogen/progestogen ratios in the OCs) |
| **Gall Bladder Disease** | | | |
| RCGP, 1982 | Gallbladder disease | "estrogen" 50, 100–150 | Consistent with positive trend, but exploratory only |

formed for this analysis, as was done for the majority of the other analyses performed by the RCGP,[16] and so the validity of the dose effect is questionable.

A further report from the RCGP[18] compared OCs containing estrogen levels of 100–150 mcg, 75–80 mcg and 50 mcg or less with the incidence of venous thromboembolism. No statistical difference in rates of DVT was observed, although such an association did exist for superficial venous thrombosis. The potential for bias was discussed above. One must also question a dosage effect between the occurrence of thromboembolism and OC estrogen dose in the two RCGP reports on the grounds of biological plausibility. If a true dose association existed, the mechanism would be expected to affect equally both deep and superficial venous thrombosis.

The automated recordings of all drug prescriptions filled and the diagnoses for all hospitalizations in the Group Health Cooperative of Puget Sound permitted a follow-up study to be performed on the association between OC use and venous thromboembolism for 1977 to 1979.[19] OC estrogen content was classified as 100 mcg or more, 50–80 mcg, and less than 50 mcg. Women with a history of predisposing conditions were excluded from the study. No association was found between the estrogen content of OCs and venous thromboembolism.

Vessey et al.[20] presented data from the Oxford-Family Planning Association follow-up study. Married women aged 25–39 were recruited to the study between 1968 and 1974. Although the data were too few to confirm a dose-response association, the crude risks were consistent with a reduced risk of certain/probable venous thromboembolism in women using OCs containing less than 50 mcg of estrogen as compared to those using OCs containing 50 mcg or more of estrogen. The possibilities of bias cannot be excluded, however, from this observation because:

- Women who were using higher estrogen dosage OCs may have been older than women using low dose OCs.
- Admission to hospital for the investigation of possible DVT could have been biased toward women using higher-dose OCs, because of an increased index of suspicion in such cases.
- Confounding by progestogens almost certainly occurred.

The authors made no comments about any of these possibilities.

*Hypertension*

An inverse relationship between the occurrence of hypertension and estrogen dosage was initially observed by the RCGP.[16] Women taking OCs containing 100 mcg or more of estrogen ran about one-half the risk of women taking 50 mcg preparations. This finding, however, was clearly the result of a diagnostic bias, as the authors themselves admitted. The authors concluded that there was no evidence that the dosage of estrogen was related to the incidence of hypertension.

*Gallbladder disease*

Although no excess of total gallbladder disease among OC users was identified, the rate of this disease among women using 100–150-mcg estrogen OCs was found to be more than twice that for women taking OCs with an estrogen content in the 50-mcg range.[21] As with the previous studies, progestogen confounding occurred.

## Overview

Fourteen investigations have explored the relationship between contraceptive estrogen dosages and several disease categories: venous thromboembolism, arterial thrombembolism, hypertension and gallbladder disease. Seven of these investigations attempted to assess the effect of 30–35 mcg of estrogen, but the findings have proved inconsistent. When the potential and actual sources of bias affecting these studies are considered, we can only conclude that the existence of a dose-response relationship between OC estrogen content and diseases is uncertain.

*Implications*

For physicians, the duty to inflict no harm continually competes with the duty to benefit the patient.[22] We must also, therefore, inquire if there are estrogen dose-related benefits associated with the OC so that the potential benefits may be weighed against the potential risks.

*Contraceptive efficacy:* The chief benefit of OCs is the prevention or delay of pregnancy. Pregnancy rates have been observed to increase as the abolute doses of both estrogen and progestogen in OCs decrease, although the increase may be small.[23–24]

A smaller margin of safety may exist if a 30–35-mcg pill is missed, as compared with a 50-mcg pill. This fact may be of particular importance as drug interactions can also reduce the contraceptive efficacy of OCs. Small-scale reports of increased pregnancy rates have ocurred when drugs such as rifampicin were administered to users of relatively low-dose combination OCs.[25–26] The number of drugs which may interact with OCs to reduce efficacy is large, and many of these drugs (eg., ampicillin, tetracycline) are in very common use.[27–28]

It must be remembered that the acceptability of a method of contraception (measured as the discontinuance rate) is part of the assessment of the use effectiveness of the method. In randomized clinical trials,[23–24, 29] increased rates of spotting and breakthrough bleeding have been associated with decreasing estrogen content in combined OCs containing 50 mcg or less of ethinyl estradiol. A strong association between the occurrence of spotting/bleeding and OC discontinuance has been demonstrated.[30] Because there are cultural differences in interpretating the importance and meaning of alterations in the menstrual cycle,[31] women of some ethnic groups may be particularly prone to discontinue OCs if spotting/bleeding occurs. Patients who discontinue OCs are at risk for pregnancy, and alternative methods of contraception are less efficacious in preventing pregnancy. The routine prescription of a 30–35-mcg OC for all patients will undoubtedly cause an increase in the occurrence of unwanted pregnancy for the reasons already stated. The size of the increase may be small when populations are studied, but individual family physicians deal with individual patients. To a patient, the risk may be unacceptable.

*Legal and ethical considerations:* The Committee recommendations state specifically that: "the recommended dosage of estrogen . . . is 30–35 mcg . . . 50 mcg of estrogen should . . . be used only when good cycle control cannot be attained with compounds containing 30–35 mcg . . ." Given this wording, several questions arise:

- Has the physician a legal or ethical obligation to recall immediately all pa-

tients taking OCs containing at least 50 mcg of estrogen?

- If so, what is the physician's liability if the patient cannot be located?
- What is the liability of a physician who maintains a patient on a 50-mcg OC, in the absence of a trial on a lower-dose OC if the patient incurs a major adverse event? What is the liability of a physician if a compliant patient on a 30–35-mcg OC incurs an unwanted pregnancy?

Although we have no answers for these questions, we think that they deserve careful consideration.

## Conclusions

The rationale for prescribing 30–35-mcg OCs in preference to 50-mcg-OCs is often assumed to be that of reducing the risk of major adverse effects that might be associated with higher doses of estrogen. Through our review of the literature we have shown that there is no conclusive evidence of such a dose-response relationship.

The rationale for the selection of OCs should follow that basic principle of therapeutics: prescribe the minimum dose of any drug to achieve the desired effect and to cause minimum side-effects. For many patients this means that a 30–35-mcg OC is appropriate. For some patients, however, particularly those who are taking-long term courses of antibiotics or who may be particularly prone to forgetting pills, a 50-mcg OC is preferable. ◉

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